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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/684,554	10/06/2000	John F. Engelhardt	875.024US1	4157

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EXAMINER	
WINKLER, ULRIKE	13

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/684,554	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *2,3,8,12-18,21,23-45 and 48-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,9-11,19,20,22,46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 October 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *12* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of Group VII in Paper No. 11 is acknowledged. The traversal is on the ground(s) that inventions are so closely related on the basis of the invention that they do not pose a serious burden to search and therefore should be searched together. This is not found persuasive because promoters differ structurally and functionally from enhancers and other functional regions. Promoters are regions of DNA that are recognized by RNA polymerase, while enhancers boost the transcription of DNA. The location of enhancers may be at distant points in the DNA. Therefore, the search for one structure does not necessarily encompass a complete search of the other structure. The structures have been placed in different groups for this reason. It should be noted that the groups have been indicated as being linked by the central core structure found in the composition of claim 1. Therefore, if the composition of claim 1 is not found in the prior art the linked inventions will be rejoined.

Applicant may always go on the record stating unequivocally that the structures separated into the various groups in the Election/Restriction requirement are obvious variants of one another.

In order to facilitate the prosecution of this application, Applicant is requested to cancel all non-elected embodiments from the claims.

Newly submitted claims 49-54 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The newly added claims are grouped with Group X as being drawn to a method of transferring the recombinant DNA composition to a host cell. Applicant is advised that a rejoinder of claims is possible at a later date if the product is eventually found patentable. Guidance on treatment of product and process

claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. §103(b) is set forth in the Commissioner's Notice of February 28, 1996 published on March 26, 1996 at 1184 O.G. 86.

Upon review of the newly amended claim 19 a telephone call was made to applicant (Paper No. 12) indicating that in view of the amendments the elected group VII would be rejoined with another group and requested that applicant elect another group for prosecution on the merits. Applicant returned the telephone call on March 4, 2002 indicating that Group II is now elected to be rejoined with Group VII.

Therefore, claims 1, 4-7, 9, 10, 11, 19, 20, 23, 46, 47 are under consideration in the instant Office Action.

Sequence listing

Applicant's CRF and paper sequence listing have been entered.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, Paper No. 5, is attached to the instant Office Action.

Drawings

The drawings are objected to, please see Notice of Draftsperson's Review attached to the instant Office Action. Correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4-7, 9-11 and 46, 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Engelhardt et al. (U.S. Pat. No. 6,436,392 B1).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

The instant invention is drawn to a composition comprising two recombinant adenovirus vectors.

> MPEP 2111.03 The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *Moleculon Research Corp. v. CBS*, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

The composition requires two recombinant AAV constructs that comprise a 5'and 3' ITR with a heterologous DNA sequence in between (claims 1 and 19). The vectors comprise a promoter (a heterologous transcriptional element) linked to the open reading frame (claims 4, 9, 11, 19, 46 and 47). The composition of one of the recombinant AAV vectors requires a splice donor site at the 3' end of the open reading frame (claim 5). The heterologous transcriptional regulatory element of one rAAV is able to regulate the expression of another gene (claim 19). The functional limitation (claim 19) only requires that the vector comprises sequences that can regulate another gene sequence.

The host cells of the patented methods comprises at least two recombinant AAV vectors each comprises a 5' and 3' LTR, a heterologous DNA segment (open reading frame). Additionally, one vector comprises a splice acceptor site and the other vector comprises a splice donor site. Therefore, the instant invention is anticipated by Engelhardt et al.

Claims 1, 4-7, 9-11, 46 and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Couto et al. (U.S. Pat. No. 6, 200,560) or Couto et al. (U.S. Pat. No. 6, 221, 349).

The instant invention is drawn to a composition comprising two recombinant adenovirus vectors. The composition requires two recombinant AAV constructs that comprise a 5'and 3' ITR with a heterologous DNA sequence in between (claim 1, 19). The vectors comprise a promoter (a heterologous transcriptional element) linked to the open reading frame (claims 4, 9, 11, 19, 46 and 47). The composition of one of the recombinant AAV vectors requires a splice donor site at the 3' end of the open reading frame (claim 5). The heterologous transcriptional regulatory element of one rAAV is able to regulate the expression of another gene (claim 19). The functional limitation (claim 19) only requires that the vector comprises sequences that can regulate another gene sequence.

The references disclose the introduction of two recombinant AAV virus vectors into a cell for the production of factor VIII (see examples 1, 11, see figure 7). These vectors are capable of delivering nucleic acid containing constructs which result in the production of full-length therapeutic levels of biologically active Factor VIII in the recipient individual in vivo. The heavy and light chains of human Factor VIII (hFVIII) were assembled and cloned as expression cassettes into AAV vectors. Both vectors contain the promoter and the first non-coding intron (from -573 to +985) from the human elongation factor 1.alpha. (EF1.alpha.) gene (EF1alpha promoter and first intron). Each vector also contains the first 57 base pairs of the FVIII heavy chain encoding the 19 amino acid signal sequence. The heavy chain construct encodes the A1 and A2 domains and 5 amino acids from the N terminus of the B domain. The light chain vector encodes 85 amino acids of the carboxy terminal B domain, in addition to the A3, C1, and C2 domains. Both vectors utilize the human growth hormone (hGfl) polyadenylation signal. The expression cassettes were inserted between AAV ITRs. The removal of introns requires the

presence of a splice donor and a splice acceptor site. The transcription of both vectors was assayed (see examples 12) in the liver of mice. Therefore, the instant invention is anticipated by Couto et al.

Claims 1, 4, 5, 9-11, 19, 20, 22, 46 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Rendahl et al. (Nature Biotechnology 1998).

The instant invention is drawn to a composition comprising two recombinant adenovirus vectors. The composition requires two recombinant AAV constructs that comprise a 5'and 3' ITR with a heterologous DNA sequence in between (claims 1 and 19). The vectors comprise a promoter (a heterologous transcriptional element) linked to the open reading frame (claims 4, 9, 11, 19, 46 and 47). The composition of one of the recombinant AAV vectors requires a splice donor site at the 3' end of the open reading frame (claim 5). The heterologous transcriptional regulatory element of one rAAV is able to regulate the expression of another gene (claim 19). The functional limitation (claim 19) only requires that the vector comprises sequences that can regulate another gene sequence.

Rehndahl et al. disclose the *in vivo* regulation of gene expression following co-injection of two separate recombinant adeno-associated virus vectors, one encoding an inducible murine erythropoietin transgene (a therapeutic gene) and the other a transcriptional activator, directly into the skeletal muscle of adult immunocompetent mice. Construct one (rAAV-CMV-tTA) comprises the tetracylince responsive transactivator and the mouse protamine polyadenylation site and mRNA splice donor/splice acceptor. Vector two (rAAV-(tetO)7-minCMV-mEPO) tetracycline responsive element reiterated 7 times regulating the minimal CMV promoter bovine

growth hormone polyadenylation site. In this instance the expression from one rAAV regulates the expression of genes in another rAAV. The vectors are shown to be expressed in the same cells. Therefore, the instant invention is anticipated by Rendahl et al

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4-7, 9, 10, 11, 46, 47 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-15 of U.S. Patent No. 6,436,292. The host cells of the patented methods comprises at least two recombinant AAV vectors each comprises a 5' and 3' LTR, a heterologous DNA segment (open reading frame). Additionally, one vector comprises a splice acceptor site and the other vector comprises a splice donor site. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant invention does not exclude the compositions used in the patented methods.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D.

JAMES HOUSEL 3/8/03
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600